

Breast Cancer Res Treat (2013) 142:603–609
DOI 10.1007/s10549-013-2734-4

EPIDEMIOLOGY

Use of the metastatic breast cancer progression (MBC-P) questionnaire to assess the value of progression-free survival for women with metastatic breast cancer

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Received: 8 July 2013 / Accepted: 12 October 2013 / Published online: 12 November 2013
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Abstract While overall survival (OS) has historically been the primary endpoint for clinical trials in oncology, progression-free survival (PFS) has gained acceptance as a valuable surrogate endpoint. However, there are no known published reports about the value of PFS from the patient's perspective. We developed a questionnaire that included items regarding quality of life (QoL) and the importance of different treatment outcomes and presented hypothetical scenarios for which respondents were asked to indicate their preferences concerning treatments as they relate to PFS. 282 women with metastatic breast cancer (MBC), ranging in age from 21 to 80 years completed an online version of this questionnaire. The majority of women (66 %) had been diagnosed with MBC within the previous 3 years and 56 % had been told their MBC had progressed. When asked to rank five treatment characteristics from most important to least important,

respondents ranked “extending PFS” as the second most important treatment outcome after OS. When presented with a hypothetical scenario of two women receiving different treatments, respondents preferred the treatment that resulted in longer PFS (16 vs. 12 months), even when OS and side effects were assumed to be equal. Specifically, when asked to consider which woman within the hypothetical scenario had better QoL, physical functioning, and emotional well-being, respondents more often chose the woman who experienced longer PFS (QoL: 40 vs. 6 %; physical functioning: 32 vs. 8 %; emotional well-being: 58 vs. 6 %) compared to the woman within the hypothetical scenario who had a shorter time of progression. Respondents rated their own QoL highest after being told their MBC was responding to treatment (mean score 76.6) versus after the initial diagnosis of breast cancer and MBC (68.5 and 60.3). These findings suggest that extending PFS is an important treatment outcome and, from a patient perspective, improves overall QoL, physical functioning, and emotional well-being.

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Keywords Metastatic breast cancer · Progression-free survival · Quality of life · Questionnaire

Introduction

While overall survival (OS) is often the preferred endpoint measured in oncology trials, progression-free survival (PFS) has become more common as an endpoint of primary or secondary interest, in part because of the additional time needed to assess OS [1–6]. While OS estimates can be impacted by post-progression treatment heterogeneity and crossover [7], PFS provides a direct measure of treatment effect on the course of disease that is not susceptible to

such bias. While PFS, from a clinician's perspective, measures the amount of time before the disease progresses, research regarding its value from a patient's perspective is limited. One recently published study reported that patients with renal cell carcinoma consider PFS to be an important outcome, and that they are willing to accept higher treatment-related risks to increase their PFS [8]. However, no published literature on the value of PFS from the perspective of patients with metastatic breast cancer (MBC) has been found.

The value of PFS can be difficult to quantify since many variables play a role in determining both OS and the quality of a patient's life during this period of time. However, measures of emotional well-being and quality of life (QoL) can help describe the value of PFS, and are common metrics in oncology studies [9–13]. While better QoL has been shown to be associated with longer OS for cancer patients [14, 15], there are no published data describing the association of QoL or emotional well-being with PFS.

The goal was to conduct a multi-stage study in which we would first conduct concept elicitation interviews of patients with MBC, use the findings from this qualitative research to draft a questionnaire, pilot test the questionnaire to finalize it, and then implement the final questionnaire in a study. We sought to obtain data regarding the value of PFS in patients with MBC, to describe the gain in value from PFS, and to investigate how that value differed across relevant patient and clinical characteristics.

Methods

Study protocol and selection of participants

The study was conducted in three consecutive parts. Parts I and II involved the creation and pilot testing of a newly developed self-administered questionnaire, and then data were collected online from respondents with MBC during Part III. For all parts of the study, eligible patients were female, at least 18 years of age, with a clinical diagnosis of MBC, able to speak and read English and willing to sign an informed consent form. Patients eligible for Part III also had to be willing to self-administer the online questionnaire. The study was approved by a central institutional review board. Patients from the United States were recruited using internet advertisements for the study posted on websites devoted to breast cancer.

One-on-one in-depth interviews with women with MBC

During Part I, one-on-one in-depth telephone interviews were conducted with 19 women with MBC to determine

important issue areas related to PFS from a patient's perspective. While the diagnosis of MBC had significantly impacted all areas of QoL for those interviewed, the emotional impact (anxiety, depression, isolation, fear, feeling down, and uncertainty) was noted by all, but one, of the 19 women interviewed. Additionally, of the 8 whose disease had not progressed, 5 indicated that they would likely be more aggressive with their treatment if they were to learn their cancer had progressed. The vast majority of the 11 whose disease had progressed were more willing to accept side effects of more aggressive treatments (specific number not available). When asked about the most important ways metastatic cancer currently affects their lives, aspects such as being consumed with doctor appointments, managing side effects of treatment, limitations in ability to work or get around, and impact on family members as well as emotional aspects were often mentioned. Finally, the value placed on PFS varied and was clearly affected by many factors, including age and progression status. Nearly all of the progressed women felt they would be willing to explore a treatment option that would give them 4 months of PFS, whereas those in the non-progressed group provided mixed responses. Based on this information, a self-administered questionnaire was developed. The questionnaire was pre-tested in Part II with a subset of the women (8 of the 19) who took part in the Part I interviews. Minor modifications were made to the questionnaire, and a final version of the MBC-Progression (MBC-P) questionnaire was developed for use in Part III.

Overview of the MBC-P questionnaire

The final version of the MBC-P included items assessing overall health and well-being, cancer worry, and impact on patients' physical and emotional status (energy levels, social isolation, activity restrictions, limitations, etc.) as well as the hypothetical scenario regarding PFS. Many of the impact questions were presented in the form of agreement statements, and participants were asked to respond to each statement using a scale ranging from 1 (strongly agree) to 5 (strongly disagree). Examples of these statements include, "I can live with side effects as long as treatment is working," and "The length of time I have before my disease progresses is more important to me than the quality of my days." Several types of data were collected: respondents provided information on their own health and well-being; they reflected on QoL and well-being associated with their own treatment; and they offered their opinion regarding the experience of two women in a unique hypothetical scenario. Specifically, respondents

Table 1 Demographic and clinical information of Part III respondents ($n = 282$)

	<i>n</i>	%
Age		
Mean, SD	50.2 (10.8)	
Range	21–80	
Age <50 (<i>n</i> , %)	128	45.4
Age ≥50 (<i>n</i> , %)	154	54.6
Race/ethnicity (<i>n</i> , %)		
Caucasian/White	249	88.3
Latino or Hispanic	6	2.1
African American/Black	16	5.7
Asian or Pacific Islander	7	2.5
Native American or Alaskan native	1	<1
Other	3	1.1
Highest education (<i>n</i> , %)		
High school degree or GED or less	25	8.9
Some college	61	21.6
College degree	107	37.9
Graduate or professional degree	86	30.5
Other	3	1.1
Breast cancer first diagnosed (<i>n</i> , %)		
<1 year ago	48	17.0
1–5 years ago	108	38.3
>5 years ago	128	45.4
Time since MBC first diagnosed (<i>n</i> , %)		
<1 year ago	89	31.6
1–3 years ago	96	34.0
>3 years ago	97	34.4
Ever told MBC progressed? (<i>n</i> , %)		
Yes	159	56.4
No	123	43.6

were presented with a hypothetical scenario in which one woman (Woman A) receives treatment X for 1 year (12 months) before her cancer progresses, while another woman (Woman B) receives treatment Y for 1 year and 4 months (16 months) before her cancer progresses. Respondents were further told that OS and side effects were equivalent for the two women, and were then asked to consider which woman had higher overall QoL, physical functioning, and emotional well-being. The precise wording of the hypothetical scenario posed, as well as additional examples of items from the MBC-P, appear in [Appendix](#). The MBC-P contained a total of 41 items and took approximately 15 min to complete. It was administered online between January and May of 2011. Completed online entries were thoroughly screened to ensure that multiple surveys from the same computer (IP address) were not included.

Table 2 Statements most strongly agreed with by respondents

Statement	Mean (SD) score ^a	95 % CI
I can complete tasks in a timely manner	2.73 (1.23)	[2.59, 2.88]
I can accomplish what I like to get done	2.70 (1.19)	[2.56, 2.84]
I have had enough energy	2.65 (1.07)	[2.52, 2.77]
I have felt hopeful about the future	2.59 (1.11)	[2.46, 2.72]
I can take care of myself	2.28 (1.15)	[2.14, 2.42]
I can put some aspects of my life on hold	2.09 (1.12)	[1.96, 2.22]
I enjoy every day to the fullest	2.01 (1.01)	[1.89, 2.13]
I can live with side effects as long as the treatment is working	1.74 (1.00)	[1.63, 1.86]

^a Responses range from 1 (strongly agree) to 5 (strongly disagree)

Statistical analysis

Statistical analysis was performed on data collected in Part III. Means, standard deviations, and ranges were calculated for continuous variables such as age and length of time since MBC diagnosis, as well as for survey items where patients provided ranked or rated responses. Frequencies and percentages were calculated for categorical data, and some measures were stratified by disease progression, age, or time since MBC diagnosis. Since these outcomes were exploratory in nature and intended to drive future hypotheses, only a few statistical comparisons were made using independent sample *t* tests, analysis of variance or χ^2 tests. Differences were considered statistically significant at the 0.05 level. Otherwise, descriptive results, without testing for statistical differences, are presented. All analyses were performed using SPSS, version 19.0.

Results

Study population

A total of 547 people initiated the online survey for Part III. From this initial set of respondents, 265 were deemed ineligible for the following reasons: incomplete entries ($n = 144$), duplicate entry ($n = 101$), male ($n = 7$), did not provide consent ($n = 5$), or for other eligibility issues ($n = 8$). The remaining 282 women with MBC were deemed eligible and completed the online survey. Demographic and clinical information on these 282 patients is provided in [Table 1](#). The mean age of respondents was 50 years and ranged from 21 to 80 years of age. Respondents were primarily white (88 %), and the majority (90 %) had at least some college education. Nearly half of the participants (45 %) were first diagnosed with breast cancer more than 5 years ago, and roughly two-thirds (68 %) were first

Table 3 Responses to the hypothetical scenario

	All <i>n</i> , % (95 % CI)	Non-progressed <i>n</i> , % (95 % CI)	Progressed <i>n</i> , % (95 % CI)	<i>p</i> value ^a
Which woman has better QoL?				
Woman A	16, 5.7 % (3.5 %, 9.1 %)	4, 3.3 % (1.3 %, 8.1 %)	12, 7.6 % (4.4 %, 12.8 %)	0.284
They are the same	151, 53.9 % (48.1 %, 60.0 %)	66, 54.1 % (45.3 %, 62.7 %)	85, 53.8 % (46.0 %, 61.4 %)	
Woman B	113, 40.4 % (34.8 %, 46.2 %)	52, 42.6 % (34.2 %, 51.5 %)	61, 38.6 % (31.4 %, 46.4 %)	
Which woman has better physical functioning?				
Woman A	22, 7.9 % (5.3 %, 11.8 %)	5, 4.1 % (1.8 %, 9.3 %)	17, 10.8 % (7.0 %, 16.9 %)	0.079
They are the same	167, 59.6 % (54.6 %, 66.1 %)	73, 59.8 % (51.4 %, 68.6 %)	94, 59.5 % (52.8 %, 68.0 %)	
Woman B	87, 31.1 % (26.3 %, 37.2 %)	43, 35.2 % (27.6 %, 44.4 %)	44, 27.8 % (21.9 %, 35.9 %)	
Which woman has better emotional well-being?				
Woman A	17, 6.1 % (3.9 %, 9.6 %)	5, 4.1 % (1.8 %, 9.4 %)	12, 7.6 % (4.4 %, 12.9 %)	0.489
They are the same	99, 35.4 % (30.3 %, 41.5 %)	44, 36.1 % (28.6 %, 45.6 %)	55, 34.8 % (28.0 %, 42.8 %)	
Woman B	161, 57.5 % (52.2 %, 63.8 %)	71, 58.2 % (50.2 %, 67.6 %)	90, 57.0 % (49.5 %, 64.8 %)	

^a Represents *p* value for comparison of distribution between progressed and non-progressed groups

diagnosed with MBC more than a year ago. Over half (56 %) had been told that their MBC had progressed.

Agreement statements

Table 2 displays the mean scores of the most strongly agreed with statements (lower scores indicate stronger agreement on average). Statements respondents agreed most strongly with included, “I can live with side effects as long as the treatment is working” (mean = 1.74), “I enjoy every day to the fullest” (2.01) and “I can put some aspects of my life on hold” (2.09). For many of the statements, some differences were observed (though not statistically significant) based on the patients’ demographic and clinical information. For example, respondents diagnosed more recently more often strongly agreed that they could live with side effects and put some aspects of their life on hold, as compared to those who were diagnosed more than 3 years ago. Those diagnosed >3 years ago also agreed less often with the statement “I can take good care of myself.” Older patients (those aged 50+) agreed slightly more frequently with statements about feeling hopeful about the future (2.5 vs. 2.7), having enough energy (2.6 vs. 2.7), and enjoying every day to the fullest (1.9 vs. 2.2) than did younger patients.

Hypothetical scenarios

When asked to consider QoL, physical functioning, and emotional well-being for two women in a hypothetical scenario, the large majority of respondents indicated either that these measures were the same for each woman or that Woman B’s were superior to Woman A’s. For QoL, 40 % of respondents felt that Woman B had higher QoL, 6 % felt that Woman A’s QoL was higher, and 54 % felt they were the same

(Table 3). A similar pattern was seen for physical functioning: more respondents indicated that Woman B’s physical functioning was better than Woman A’s (31 vs. 8 %), while 60 % indicated that physical functioning was the same (Table 3). Finally, the majority of respondents (58 %) reported that Woman B had better emotional well-being than Woman A (Table 3), a finding that was observable regardless of progression status (among progressed: 57 %, not progressed: 59 %), age (<50: 58 %, 50+: 58 %) or time since progression (<1 year: 55 %, 1–3 years: 59 %, >3 years: 61 %).

Respondents who were diagnosed with MBC more recently (<1 year ago) were significantly more likely to perceive differences in the overall QoL for the two women ($\chi^2 = 10.02$; $df = 4$; $p = 0.04$) as compared to respondents diagnosed more than 1 year ago. In addition, respondents who were at least 50 years old (vs. those <50, $\chi^2 = 9.94$; $df = 2$; $p = 0.007$) and those with greater than 3 years since MBC diagnosis (vs. those <3 years, $\chi^2 = 7.17$; $df = 2$; $p = 0.028$) were more likely to rate the physical functioning the same for Woman A and Woman B. There were no significant differences in treatment preference by age or whether their disease had progressed.

When asked which treatment scenario (X or Y) they would prefer, the majority of respondents [63, 95 % CI (56.9, 68.2 %)] preferred Treatment Y (i.e., longer time before progression) over Treatment X. One-quarter [26, 95 % CI (21.0, 31.3 %)] were unsure of their preference, and 12 % [95 % CI (8.2, 15.7 %)] of respondents indicated they preferred the treatment with a shorter time to progression (p value <0.001).

Importance of treatment characteristics

When asked to rank five treatment characteristics from the most important (1) to the least important (5), respondents indicated

Table 4 Mean QoL ratings at time of initial breast cancer diagnosis, MBC diagnosis, and time of progression

	Overall Mean (SD)	Non-progressed Mean (SD)	Progressed Mean (SD)
Overall QoL			
Initial diagnosis of breast cancer (<i>n</i> = 279)	68.5 (30.1)	66.6 (30.8)	70.0 (29.5)
MBC diagnosis (<i>n</i> = 120) ^a	60.3 (30.9)	59.1 (31.0)	61.2 (31.0)
MBC progression (<i>n</i> = 174)	58.4 (27.8)	N/A	60.4 (26.7)
MBC responding (<i>n</i> = 231)	76.6 (17.7)	78.0 (15.7)	75.7 (18.9)
Physical functioning			
Initial diagnosis of breast cancer (<i>n</i> = 279)	73.7 (27.3)	74.2 (25.2)	73.2 (28.9)
MBC diagnosis (<i>n</i> = 120) ^a	63.2 (26.2)	61.9 (25.9)	64.3 (26.4)
MBC progression (<i>n</i> = 174)	61.3 (26.1)	N/A	62.4 (25.4)
MBC responding (<i>n</i> = 231)	71.0 (20.4)	71.1 (19.4)	71.0 (21.1)
Emotional well-being			
Initial diagnosis of breast cancer (<i>n</i> = 279)	60.4 (32.4)	59.7 (31.9)	61.0 (32.9)
MBC diagnosis (<i>n</i> = 120) ^a	50.7 (30.3)	46.1 (29.6)	53.9 (30.4)
MBC progression (<i>n</i> = 174)	50.5 (28.2)	N/A	51.7 (27.7)
MBC responding (<i>n</i> = 231)	76.8 (18.2)	78.3 (15.7)	75.9 (19.7)

Ratings range from 0 to 100, where 0 represents the worst you can imagine and 100 the best you can imagine

^a Excludes those whose initial diagnosis was MBC

that extending survival was the most important aspect to consider (mean ranking: 1.7 ± 1.1), followed by extending time to progression (2.4 ± 1.1), reducing the size of the tumor (2.9 ± 1.3), limiting side effects (3.0 ± 1.3), and finally the frequency of treatment (4.5 ± 1.1). The same rank order was observed regardless of disease progression status, age, or time since MBC diagnosis, with the exception of those diagnosed >3 years ago. Those patients indicated a slight preference for limiting side effects (2.8) over reducing the size of the tumor (3.0). There were no statistically significant differences by disease progression, age, or time since MBC diagnosis.

QoL ratings

Patients rated their own QoL, physical functioning, and emotional well-being at different stages of their disease using a scale ranging from 0 to 100, with 0 being the worst and 100 the best. Table 4 shows that ratings of overall QoL were higher after the initial breast cancer diagnosis (68.5) than after MBC diagnosis (60.3) or when patients were told that their MBC had progressed (58.4, *p* value <0.001). The highest QoL ratings were after respondents were told that their MBC was responding to treatment (range 75.7–78.0). Ratings for overall QoL and physical functioning for each progression level were consistently higher than ratings for emotional well-being. Emotional well-being was higher after initial breast cancer diagnosis (60.4) than after MBC diagnosis (50.7) or MBC progression (50.5).

Respondents who were diagnosed with MBC >3 years ago reported significantly higher overall QoL (*p* = 0.032),

physical functioning (*p* = 0.002), and emotional well-being (*p* = 0.027) after being told their MBC had progressed, compared to those who were diagnosed <3 years. When stratified by age, emotional well-being was significantly higher after the initial diagnosis for respondents ≥ 50 years old (*p* = 0.038) compared to those who were younger. Older respondents also reported significantly higher overall QoL (*p* = 0.001), physical functioning (*p* = 0.001), and emotional well-being (*p* = 0.027) compared to those <50 years of age, during the timeframe after being told their MBC had progressed. Finally, after being told that their MBC was responding to treatment, respondents ≥ 50 years of age reported higher overall QoL (*p* < 0.001), physical functioning (*p* < 0.001), and emotional well-being (*p* < 0.001) than respondents <50 years of age.

Discussion

Findings from this study demonstrate several important aspects of the MBC population. First, it is clear that the perceived QoL of these patients is directly correlated with the status of their disease progression as well as whether they are responding to treatment. Age and the time since cancer diagnosis also appear to affect their perception of overall QoL. Women who were younger rated their QoL as lower, as did those who were more recently diagnosed, possibly indicating that patients who have lived with MBC for a longer period of time do not experience the drop in QoL that a newly diagnosed patient experiences. At the

same time, patients strongly agreed with statements reflecting a positive emotional state, including “I feel hopeful about the future” and “I enjoy every day to the fullest.” This implies that while their emotional well-being may be affected by changes in their disease status (e.g., negatively by MBC progression or positively by response to treatment), in general these patients report experiencing a relatively high level of QoL. It is difficult to know how this compares to other MBC populations, as the literature on patients with MBC is limited.

In terms of their own treatment, patients strongly agreed that they could “live with side effects as long as the treatment is working” and “put some aspects of my life on hold.” The fact that patients indicate a willingness to endure side effects and delay or eliminate aspects of their life for a treatment that “is working” (i.e., one that extends OS or PFS) demonstrates the relative value patients place on these outcomes. Accordingly, when asked to rate the relative importance of five characteristics of their cancer treatment, extending OS and PFS were rated as the first and second most important, on average. Both aspects were rated as being more important than decreasing tumor size or side effects, suggesting that patients are willing to endure some side effects to improve overall treatment outcomes.

When presented with a hypothetical scenario of two different treatments for two different women, the majority of respondents (63 %) preferred the treatment with a longer time before disease progression (16 vs. 12 months). This suggests that patients consider four additional months of PFS as an important difference, even when there is no difference in side effects or OS for the two treatments. While it is not clear why some patients (12 %) preferred the treatment with a shorter time before disease progression, it is possible that they did not consider all aspects of the scenario (i.e., that the treatments had similar side effect profiles) or did not fully understand the exercise. If it was due to a lack of understanding of the scenario or terminology of PFS, it has important implications for physician–patient communication when it comes to decisions regarding treatment and outcomes. When asked about specific aspects of the hypothetical patients’ experience, a majority of respondents (58 %) felt that the woman whose treatment had longer PFS had better emotional well-being. This is noteworthy considering the emotional impact MBC can have on patients, as mentioned above. While it is true that most respondents felt that overall QoL (54 %) and physical functioning (60 %) were the same for both women, 40 % felt that the woman with 4 months longer PFS had higher overall QoL and 31 % felt the woman had better physical functioning. However, patients diagnosed more than a year prior did not perceive this difference in QoL again possibly due to their own experiences with disease progression and its effect on QoL.

There are several limitations to our research that should be considered. While there are benefits in collecting data using an online survey, issues such as access and technology-related challenges can impede the ability to include a representative sample. Additionally, since women in our study were well enough to complete the questionnaire, they may have been in better general health than a typical patient with MBC. Respondents were asked to retrospectively rate their QoL during previous time periods, so it is possible that there may be some recall bias. Additionally, responses reflect the perceived impact on QoL. Information on treatment therapies (e.g., the type of chemotherapy agent) was not collected, nor was the type of breast cancer. Finally, the majority of the Part III sample was white (88 %) and all patients (per eligibility criteria) were English-speaking, again calling into question the generalizability of these results and limiting our ability to investigate potential differences across race categories.

Future research, including the development of scale scores to replace the individual item-level data as currently presented, would be worthwhile. Additionally, it would be of value to confirm these results in a larger, more diverse sample of women with MBC, and eventually in a prospective study. We also plan to investigate the value of PFS in different subtypes and clinical presentations of breast cancer.

Conclusions

This is the first study designed to understand the value women with MBC place on PFS. The MBC-P questionnaire was developed with input from women with MBC and shows promise in its ability to provide a subjective measure of the importance of PFS. Respondents in our study considered PFS an important aspect of treatment and associated an additional 4 months of PFS with better overall QoL, physical functioning, and emotional well-being. To our knowledge, this is the first study to demonstrate a correlation of PFS with patient-reported QoL.

Acknowledgments This study was supported by Genentech, Inc. The authors acknowledge the contributions of Craig Solid for assistance in the preparation of this manuscript.

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Appendix: Sample Items from the MBC-P

Overall health and well being

During the past week, on how many days did the following apply to you?

- My health put stress on my relationships.
- I did not feel like being around other people.
- I felt hopeful about the future.

Cancer worry

Overall, how much to you agree or disagree with each statement?

- I feel like bad news about my cancer is just around the corner.
- I feel confident that my current treatment will prevent my cancer from progressing further.
- It is difficult to think about anything other than my cancer.

Limitations

During the past week, how much were you limited in your ability to...

- be away from home for more than a day?
- think clearly?
- spend time with family or friends?

Hypothetical scenario

“Please think about the following hypothetical situation. Your doctor suggested a particular treatment for metastatic breast cancer. Let’s call it Treatment X. Imagine Treatment X can have two outcomes:

Outcome #1: Treatment X works for one year before your cancer progresses and you have to switch to a new treatment. You could have fewer or more side effects with this new treatment.

Outcome #2: Treatment X works for one year and four months before your cancer progresses and you have to switch to a new treatment. You could have fewer or more side effects with this new treatment.

Imagine the side effects from Treatment X and your survival are the same with both outcomes.

Q: Which outcome would allow you to have better overall functioning at the end of Treatment X?

Q: Which outcome would allow you to have better overall well-being at the end of Treatment X?

Q: Which outcome would you prefer?

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